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Chronic Total Occlusion SHOULD be Treated with Coronary Artery Bypass Grafting

Zakkar: CTO should be treated with CABG

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Abstract:

Treatment of chronic total occlusion (CTOs) should be considered if associated with symptoms or evidence of myocardial viability. Historically, treatments of CTOs in the contest of multivessel (MVD), left main stem (LMS), and/or left anterior descending (LAD) disease have been via coronary artery bypass grafting (CABG-CTOs). Yet, over recent years, a vast amount of literature is showing that in North America, Europe, and Japan CABG-CTOs are being treated percutaneously (CTO-PCI). The evidence-based medicine SYNTAX trial confirms the superiority of CABG at 1 and 5 years in MACCE events across all the patient categories, including large subsets of CTO patients. This superiority appears disproportionate for patients with high SYNTAX score or with CTOs. This is in keeping with a large body of evidence favouring the use of CABG-CTOs for these anatomical categories.

The use of CTO-PCI for surgical anatomical categories is based on questionable evidence derived from "comfortable" comparisons between successful vs. failed CTO-PCI procedures, with no controls. These comparisons suggest, in fact, that CTO-PCI might be causing significant harm to patients suffering procedural failures. This safety aspect seems to be grossly misrepresented in the literature, against a disproportionate emphasis on CTO-PCI efficacy often softly defined as "on table successful recanalization", which is neither synonymous of improved myocardial perfusion/function nor evidence of late patency. This is a word of caution on the indication for PCI-CTO in "surgical" patients and on the need to address the safety and the efficacy of CTO-PCI via rigorous research.

1. Introduction

Coronary artery chronic total occlusions (CTOs) are an exacerbation of stable coronary artery disease (CAD) with advanced calcification. CTOs are defined as 100% coronary occlusions with thrombolysis in myocardial infarction (TIMI) 0 flow persisting for > 3 months [1]. National database registries and large single centre series suggest that in patients with CAD the overall incidence of CTOs may vary from 16-19% in Japan[2] to 29-33% in North America[3], suggesting that this is a prevalent problem globally. Treatment of CTOs should be considered if associated with symptoms and/or viable/ischemic myocardial territories. Historically, treatments have been via coronary artery bypass grafting (CABG) or medical therapy [3-9].

The use of percutaneous coronary intervention (PCI) to treat CTOs (CTO-PCI) against established practice is controversial[10]. This controversy is facilitated by poor evidence available and by lack of clarity in the European and American guidelines for revascularization including those for patients with stable CAD[11-15]. However, the lack of robust evidence and unclear guidelines can lead to ill-defined clinical indications determining serious geographical discrepancies in CTO-PCI medical practice. In a recent report from Japan more than 61% of patients diagnosed with CTOs (19% of all CAD patients) were treated with CTO-PCI[2]. This is a significant increase compared with a previous report from North America in which only 6-9% of all CTOs (29-33% of all CAD cases) were treated with CTO-PCI (range 1% to 16% by geographical area/centre)[3]. The report by Yamamoto and co-workers[2] suggests a widespread use of CTO-PCI in patients with multivessel CAD. This is likely to be at the expense of more established treatments such as CABG. The difference in CTO-PCI practice observed between Japan and North America is not easily explained. Contributing factors may be differences in study period, unclear guidelines, misrepresentation of safety/efficacy evidence supporting the use of CTO-PCI, neglect of the evidence

supporting more established treatments, gatekeeper effect, as well as the lack of policies by health authorities.

In this article we provide evidence to support the view that CABG surgery remains the gold standard for the treatment of CTOs in patients with isolated left main stem (LMS), left anterior descending (LAD) or with CTOs in the context of multi-vessel CAD. In addition we explore safety and efficacy concerns behind the widespread use of CTO-PCI.

2. Baseline determinants of health outcome and decision making in patients with CTOs

For patients with CTO the decision making process should be based on a meticulous evaluation of the coronary anatomy, the complexity of each patient risk profile, the support of the Heart Team, the reference to evidence-based medicine, and on a fully informed patient.

Clinical and cardiac specific variability of patients with CTOs

Patients with CTOs may have a complex risk profile with higher incidence of diabetes mellitus, multi-vessel disease (MVD), LMS coronary disease, diffuse coronary and peripheral vascular disease, and aggressive calcification of their coronary vessels resulting in higher SYNTAX scores[16, 17]. Additional variability may derive from differences in cardiac risk factors such as presence of single or multi-vessel CAD, extensive left ventricular (LV) scarring and/or residual viability/hibernation in the CTO territory, which may reflect on LV function[18, 19], ischemic burden (if any), and symptoms status (asymptomatic or chronic stable angina)[20, 21].

Coronary anatomical variability of CTOs

The anatomical assessment of CAD is based on coronary angiography. However, with CTOs often the affected coronary artery is poorly seen via retrograde filling from collaterals. This may trigger a degree of uncertainty of its quality and size. Contrast computer tomography

may however provide information on the severity and distribution of coronary calcification and length of CTOs. Intravascular ultrasound or optical coherence tomography have no diagnostic benefits although they may be helpful during CTO-PCI. The Canadian Multicentre CTO Registry showed that only in <10% of cases an isolated CTO lesion is outside the LMS, LAD or MVD CAD context. In particular, the Registry showed that 47% of solitary CTOs occur in the right coronary artery (RCA), 20% in the LAD and 16% in the left circumflex (CX), that CTOs in more than one coronary artery were noted in 17% of the cases, and that MVD was present in 76% of patients with CTOs, of whom 7% were afflicted by LMS disease[22]. Similar distributions of CTOs have been reported by other investigators[2, 4, 22-24].

The anatomic location of CTOs within each coronary artery can be either at the proximal/mid segment or at the mid/distal segment. This may have treatment implications as PCI procedures are in the majority of cases not suitable for distal coronary segments (hence not able to treat distal CTOs) while CABG procedures are generally performed in distal coronary segments, hence able to treat both proximal and distal CTOs (Figure 1). This is supported by the inclusion criteria of both the DECISION-CTO (Drug-Eluting Stent Implantation vs Optimal Medical Treatment in Patients with Chronic Total Occlusion) and the EuroCTO (European Study on the utilization of Revascularisation vs Optimal Medical Treatment for the Treatment of Chronic Total Coronary Occlusion) trials (clinicaltrials.gov identifiers NCT01078051 and NCT01760083 respectively) which include in their angiographic inclusion criteria a target coronary size of "*2.5mm or ≥2.5mm",* hence clearly excluding patients with distal CTOs. Similarly, the EXPERT-CTO (Evaluation of the XIENCE PRIME™ LL and XIENCE Nano™ Everolimus Eluting Coronary Stent Coronary Stents, Performance, and Technique in Chronic Total Occlusions) pilot trial (clinicaltrials.gov identifiers NCT01435031) included in its angiographic inclusion criteria "*Segment not*

located in an excessively distal location". The inclusion/exclusion criteria of these studies suggests that CTO-PCI procedures target CTOs in proximal-mid coronary segments, while generally excluding those with distal coronary CTOs.

In addition, the length of CTOs may vary from few millimetres to > 40mm with long CTOs often associated with scarred/infarcted myocardium and associated with worse health outcome[23]. Long CTOs may at times affect coronary bifurcations of sizable branches and this may have implications on the treatment to select to ensure a complete and effective revascularisation of both branches.

Pathophysiology of stable CAD and CTOs

Severe atherosclerotic CAD is associated with endothelial dysfunction affecting the ability to increase blood flow in response to changing metabolic demands, hence leading to myocardial ischaemia[25, 26]. Spontaneous rupture of severely stenotic plaques and thrombotic complications often lead to MI and sudden death[27, 28], although they may also go clinically undetected due to healing of the ruptured plaque[29, 30]. However, MI and acute coronary syndromes more often occurs by rupture/thrombosis of mild/moderate plaques, suggesting that "in plaque" events play a role in sudden death and fatal MI[29, 31]. Hence, methods of coronary revascularisation should minimise the chances of additional iatrogenic "in plaque" or distal events. Given that CTO-PCIs are "in-plaque" procedures determining iatrogenic plaque ruptures during prolonged wiring/ballooning/stenting they can lead to acute thrombosis and/or distal coronary microembolisation. Hence these procedures pose potential safety concerns which need proper investigating.

3. Evidence supporting the use of CABG for the treatment of CTOs in patients with LMS, LAD, and MVD

Impact of CABG on revascularisation rates, health outcome and graft patency rates

Historically, the treatment of CTOs has been assigned to CABG or medical therapy[5-9]. The superiority of CABG surgery vs PCI-stenting in patients with MVD, LMS or impaired LV function is confirmed by the SYNTAX trial[16, 17]. This evidence-based medicine trial illustrates that treating CTOs with CABG is associated with excellent early and long-term health outcome. Hence, alternative methods of CTO revascularisation targeting this type of patients should be compared versus CABG surgery as the established standard. Data from the UK National Data Registry[32] shows that for all patients with stable and elective CAD the utilisation of a left internal mammary artery (LIMA)-LAD graft is at 95%. This is associated with a 30-day mortality of only 1.0%, as well as a postoperative incidence of stroke and reopening for bleeding of 0.9% and 2.9%, respectively. Only 0.2% of patients are re-operated for revision of grafts problems. Of note, the observed mortality has decreased markedly over time and it is consistently lower than the mortality predicted by logistic EuroSCORE[32]. In keeping with the outcome of the UK Registry a study of 21,640 patients from an USA Registry undergoing CABG with on or off pump techniques reported an in-hospital mortality rate of 2.3%, 2.1% of reoperation for bleeding, 1.5% stroke, and 0.5% perioperative MI[33]. This outcome is confirmed by a very large recent study with more than 1.5 million CABG patients also from USA[34].

In the SYNTAX trial the superiority of CABG vs PCI was obvious at 12-month for the primary outcome major adverse cardiac or cerebrovascular events (MACCE) [16]. The difference become striking at the final 5-year evaluation (MACCE 26.9% vs. 37.9%; cardiac death 5.3% vs. 9.0%, myocardial infarction 3.8% vs. 9.7% and need for repeat revascularisation 13.7% vs. 25.9%) [17]. This trial showed that patients with intermediate or high SYNTAX score (many with CTOs) disproportionately benefited from CABG[16, 17]. The 5-year rate of MACCE events of the CABG arm of the SYNTAX trial was low and

comparable to the rate of MACCE events observed in the parallel SYNTAX CABG Registry (26.9% vs 23.2% respectively). This is a remarkable finding as the CABG Registry cohort (n=644) included as many as 56.4% of patients with CTOs vs. 22.2% of the CABG arm of the trial. Yet, the rates of completeness of revascularisation, was 74.7% vs. 63.2% respectively. This finding also suggests that a rate of CTOs as high as 56.4% in CABG surgery practice does not affect long-term health outcome. This important finding derived from an evidence-based medicine trial establishes a comparative standard for CTO-PCI practice to match. The SYNTAX PCI Registry cohort (n=192) included less patients with CTOs compared to the CABG Registry (36.5% vs. 56.4% respectively) as reflected in a lower SYNTAX score (31.6±12.3 vs. 37.8±13.3). Yet, the completeness of revascularisation in this group was much lower at 36.5% vs. 74.7% of the CABG registry cohort. Hence, CABG surgery can achieve very high rate of completeness of revascularisations, regardless of the incidence of CTO lesions and of levels of SYNTAX score. This is not the case for PCI. The rate of MACCE events at 5-year between the CABG and PCI registries, both with higher incidence of CTOs compared to the trial cohorts, favoured disproportionately CABG (23.2% vs. 49.2%, respectively) [35].

Other studies focusing on CTOs patients also demonstrate excellent outcomes associated with the use of CABG. Data are available comparing the two subsets of CTO patients entered in the SYNTAX trial[35]. The trial included a total of 543 CTO patients (CABG n-266; PCI n=277) with similar coronary distribution and SYNTAX score between these two cohorts. The overall success rate for treatment of CTOs (including cases not attempted) was 68.1% vs. 49.4%, CABG vs PCI respectively. In the CABG subset 97.8% CTOs were treated with at least one arterial graft. In the PCI subset the procedure was staged in 20.3% of patients, with use of an average of 5.0±2.2 stents per patient (range 8-80mm of stents). In these sub-groups

health outcome at 12 months showed a significant difference in MACCE events at 12.2% vs. 18.9% CABG vs. PCI respectively[16].

Banerjee *et al*. [23] reported a series of 605 consecutive patients undergoing CABG, of whom 256 patients (42%) had CTOs. All LAD-CTOs (27.2% of all CTOs) were bypassed successfully (with LIMA grafts) vs. 92% of the circumflex (CX) and right coronary artery (RCA) arteries. Among patients with multiple CTOs (26.2%), 85.2% had all CTO territory bypassed. At 1-year there was no difference in the incidence of MACE events (8.0% vs. 7.8% CTO vs. non-CTO groups). However, longer CTO length (>40 mm) was associated with higher mortality at one year. The need for repeat revascularization (including PCI) was higher in the non- CTO group, although no difference was observed in need for repeat CABG (5.0% vs. 5.1%, CTO vs. non-CTO groups, respectively). Freedom from cardiac death at 1-year was significantly lower in the CTO group ($p < 0.048$). These findings are in keeping with the report by Fefer et al. [36] in a series of 405 consecutive CABG patients including 174 cases with a total of 221 CTOs, of which 86% were successfully bypassed (100% LAD-CTO bypassed successfully).

Effectiveness of LIMA-LAD graft and long-term patency rates of CABG

There is evidence in the literature that CTO-PCI is being used extensively in patients with CTO lesions of the LAD alone or in the context of MVD[2]. This is surprising when considering that the patient benefits associated with the LIMA-LAD graft have been transformational with limited in-hospital risks, improved life expectancy benefits, and very high patency rates (92-95%) at 15-20 years[37, 38]. The benefits of the LIMA-LAD grafts questions the reasons for undertaking CTO-PCI of the LAD in symptomatic patients. Confirmatory studies demonstrate improved 10-year actuarial survival rates associated with the use the LIMA conduit as opposed to saphenous vein grafts (SVG) only, making the pedicled LIMA-LAD graft the dogma of modern coronary surgery. In keeping with these

findings, other confirmatory studies suggest that not using a LIMA-LAD graft is associated with an increased risks of late MI, recurrence of angina, and need for repeat revascularisation [37, 38].

The excellent long-term patency rate of the LIMA-LAD graft is confirmed also for patients with CTO-LAD (Figure 2A and 2C). Holzhey *et al*.[39] reported a series of 1800 patients undergoing single LIMA-LAD grafts via left mini-thoracotomy on the beating heart, of whom 420 patients had LAD-CTOs. In this series 99.8% of LAD-CTOs were grafted successfully. Five-year survival rates were excellent at 90.5% and 90.4% for the CTO vs non-CTO groups respectively (p = 0.91). In addition, 5-years freedom from MACCE events was 83.2% vs. 85.5%, CTO vs non-CTO groups, respectively (p=0.64), while CTOs were not found to be predictors of late MACCE events. Accordingly, Di Giammarco and colleagues[40] reported 143 patients with isolated LAD-CTO treated with LIMA-LAD grafts on the beating heart via left anterior small thoracotomy. Thirty-day mortality was 0.7%, with no occurrence of MI, cerebrovascular accident, or need for repeat revascularization. One-year survival was 98.6%, with freedom from cardiac death at 99.3%, 100% freedom from MI, 99.3% freedom from any form of repeat revascularisation, and 97.9% freedom from MACE events. In addition, eight-year survival was 94.9%, freedom from cardiac death was 96.3%, with 99.2% freedom from MI, 94.4% freedom from any repeat revascularisation, and 92.8% freedom from MACE events. At 6-months after surgery 56% of patients had undergone control angiography with patency rates of 98.2%. Finally, the PRAGUE-4 trial in 400 patients undergoing off-pump coronary surgery showed a patency rate of CTO-LAD grafts of 100% at 1 year[41].

CABG revascularisation of CTOs with SVG grafts

One of the arguments against surgical intervention for single vessel CAD other than LAD disease is the long-term patency rates of saphenous vein grafts (SVGs). Historical data on

SVG grafts long term patency rate suggest that approximately 50% of these grafts become occluded within 10-years[37, 38]. This also means that the remaining 50% SVG grafts remain patent beyond the 10-year cut off (Figure 2B). However, more recent reports suggest SVGs patency rates of as high as > 80% at long-term follow up in some centres possibly as result of improved management of postoperative anti-platelet function, refinement of surgical approaches with utilisation of less invasive SVG harvesting techniques[42], and the a better understanding of the mechanisms involved in developing vein grafts inflammation and intimal hyperplasia[43-45]. For example, the 7-year patency rates of the BHACAS trials assessed with multi-slice CT scans showed an overall 89% patency rates in both the on-pump and off-pump groups despite utilisation of SVGs for approximately 75% of grafts[46].

Efficacy of CABG for CTOs affecting coronary vessels other than the LAD

For the rare condition of LMS-CTO (0.04-0.4% of all CTOs) small surgical series have been reported with excellent revascularisation rates and late outcome with successful use of LIMA-LAD grafts[47-49]. Successful revascularisation rates are reported at 80-90% for CTOs of LCX, with >80% of patients having all multiple CTOs treated successfully and concomitantly[23, 36]. Fefer *et al.* [36] showed that presence of CTOs was not associated with increased mortality by multivariate analysis. The study also suggested that failure to revascularize a non-LAD CTO was not associated with adverse long-term outcome.

CTOs requiring endarterectomy during CABG

Occasionally, surgeons have had to deal with complex, distal and long CTO lesions by performing more invasive procedures such as endarterectomy. Gill *et al.*[50] reported a small series of 74 patients undergoing LIMA-LAD, in whom 25 patients received endarterectomy to remove the CTO lesion prior to positioning the LIMA graft. This approach was associated with high inotropic requirement in 25% of the patients and a 6.7% incidence of postoperative

MI. This study nonetheless is unfortunately too small for any meaningful considerations. However, it is wort noting that the rates of these postoperative complications were unusually high by routine CABG standards, whilst supporting the concept that increased coronary invasiveness is associated with worse cardiac specific outcome.

4. Evidence supporting the use of PCI-stenting for the treatment of CTOs in patients with LMS, LAD, and MVD

The use of CTO-PCI is wide spreading due to advances in PCI technologies including "parallel" and "seesaw" wire techniques, balloon anchoring, sub-intimal tracking and re-entry (STAR), retrograde approach, contralateral injection, and intravascular ultrasound guidance[51]. Claims of PCI efficacy for CTO-PCIs are mostly based on observational studies comparing successful vs failed CTO-PCI recanalizations with misrepresentation of the iatrogenic effects determined by CTO-PCI undertaking in the cohorts suffering failed procedures.

Comparing successful vs failed CTO-PCIs: a fair trade-off?

Comparing successful versus failed PCI-stent for CTOs does not provide evidence of the efficacy of CTO-PCI versus other forms of revascularisation. Rather, this approach may allow ascertaining potential safety concerns based on the severity and rates of serious complications observed in the failed CTO-PCI groups. We simply do not know what would have happened to the patients suffering a failed CTO-PCI, had they been offered instead more established treatments like medical therapy or CABG. Surprisingly, despite the lack of comparisons versus real control interventions, the outcome of the successful CTO-PCI procedures is being wrongly marketed as evidence of efficacy. Jones *et al.*[52] reported retrospectively the outcome of 6996 patients treated with PCI-stent, of whom 836 (11.9%) had CTOs. The CTO-PCI success rate was suboptimal at 69.6%, with failed CTO-PCIs in

64/232 (28%) LAD-CTOs, 35/112 (31%) CX-CTOs, and 106/298 (35%) RCA-CTOs. These failures triggered a wide range of complications including coronary dissection which was much higher in the failed cases (20.5% vs. 4.9%; p < 0.0001), with 3.1% requiring urgent CABG. Multivariate analysis demonstrated that procedural failure was independently predictive of mortality (HR: 0.32, 95%CI: 0.18 to 0.58). Fang *et al.* [53] in a retrospective study in 621 CTO-PCI patients compared the outcome of PCI-stent in 551 LAD-CTOs vs. 70 ostial LAD CTOs. Ostial LAD CTO-PCIs were more complex and associated with prolonged operative and fluoroscopic time as well as increased use of contrast volumes. The European outcome of retrograde CTO-PCI procedures was reported by Galassi *et al.* [54] in 1,395 patients with 1,582 CTOs from 44 European centres. Despite the procedures were undertaken by skilled and experienced operators on table success rates were suboptimal at 70-75%. Distribution of CTO-PCI procedures included 70.4% RCAs, 7.8% CXs, 20.3% LADs, and 1.5% for combined LMS and bypass grafts. The rate of technical failure was almost 20% for LAD-CTOs, accounting for about 4.5% of all failures. Procedural failures were independent predictors of MACCE events at long term follow up (HR: 2.48; 95% CI: 1.72 to 3.57; p < 0.001). In addition, there were serious vascular complications in 16 patients, 30 cases of vessel thrombus or dissection, 4 emergency re-interventions, and 2 deaths in the failed CTO-PCI group. Disappointedly, the clinical follow-up of about one-third of the patients was missing. For the remaining two thirds of patients followed up there were major discrepancies in type and completeness of variables collected, hence providing meaningless information on the late impact of CTO-PCI. Patel *et al.* [55] performed a meta-analysis of 18,061 pooled CTO patients with 18,941 target CTOs. On table angiographic success was 77%. Early complication rates included MI at 2.5%, coronary perforation at 2.9%, tamponade at 0.3%, and contrast nephropathy at 3.8%. The use of CTO-PCI in the failed group was associated with higher rates of death (0.42% vs. 1.54%; *P*<.001). Moreover, very little data was

presented on late functional evaluations and angiographic patency rates. Galassi *et al.* [56] analysed data of 905 patients who were treated for 922 CTOs including 244 bifurcation CTOs (26.5%). The undertaking of bifurcation CTO-PCI was associated with larger use of contrast load, and higher number of stents, and a higher rate of coronary perforations compared to non-bifurcation procedures (4.9 vs. 1.7%; P<0.001), resulting in more tamponades (2.4 vs. 0.2%; P<0.001). The EXPERT CTO study has recently reported 250 CTO-PCI patients from 20 centres treated with a new generation of drug-eluted stent. Although the authors claims that the use of this stent may improve health outcome when compared with the results of previous studies it is fair to maintain that this was only a feasibility/pilot study with no control group and that the potential efficacy of the new stent will need to be ascertained in a proper head to head comparison in future trials[57].

Late functional or angiographic evidence supporting the use of CTO-PCI

Lack of functional or angiographic data is a consistent issue with CTO-PCI reports in the literature. However, anecdotal cases of early re-occlusions post CTO-PCI requiring surgical intervention are increasingly being discussed among surgeons (Figure 3A-D). Valenti and colleagues[58, 59] reported two series of CTO-PCI procedures undertaken in 258 and in 1005 consecutive patients. On-table recanalization success rates were 81% and 77% respectively. Six-nine month angiographic follow-up was available for 80% of all successful CTO-PCI procedures in both series. This showed an overall incidence of re-occlusion and/or restenosis >50% in 23.3% and 21% of patients respectively. This indicates an overall 6-9 month procedural failure (on-table failed recanalization plus late re-occlusion/restenosis) of 42.3% and 44% respectively. This angiographic data seems to raise a word of caution on the effectiveness of CTO-PCI and hopefully more robust evidence will soon be available in this area[56, 57].

One recurrent claim in CTO-PCI retrospective reports is that the procedure leads to improvement in angina symptoms, LV function and survival[20, 21]. This is based on the assumption that CTO-PCI increases the blood supply to the ischemic CTO territory (often already supplied by collaterals). However, this assumption remains unsubstantiated. In the Occluded Artery Trial (OAT) 2166 stable CAD patients with total occlusion of the infarct-related artery 3 to 28 days after MI were randomised to PCI stenting plus optimal medical therapy versus optimal medical therapy alone. This trial did not show any benefit associated with the use of PCI-stenting for the composite of death, myocardial re-infarction, or New York Heart Association (NYHA) class IV heart failure at 4-years (17.2% in the occluded artery group and 15.6% in the medical therapy group (HR 1.16; 95% CI, 0.92 to 1.45; P=0.20) while death rates were also similar (9.1% vs. 9.4%). Although the total occlusions of the OAT trial were not > 3 month chronic, hence probably easier to reopen, it's worth noting that the use of PCI-stenting was not superior to medical therapy alone. In the FACTOR trial[60] 125 patients with ischemic myocardium were treated with CTO-PCI. They completed the Seattle Angina Questionnaire at baseline and 1-month post procedure. At 1-month, in asymptomatic patients no benefit was associated to the use of CTO-PCI. This highlights the limitation of this approach in patients with ischemic myocardium but without angina, for whom a measure of prognostic outcome would be of greater value. In the COURAGE trial the impact on ischemic myocardium measured by nuclear imaging did not improve the mid-term prognosis in the PCI-stent group[6]. Accordingly, Stergiopoulos *et al*.[61] in a meta-analysis of trials in stable CAD patients with ischemic myocardium highlight that the use of PCI-stent did not improve the observed rates of death, MI, angina, and need for revascularisation compared to medical therapy. Similarly, others have suggested that CTO-PCI to LV hibernated/dysfunctional territories lead only to marginal, if any, effect even when using a sensitive imaging tool like MRI[10]. Nevertheless, the evidence of LV impairment triggered by

failed CTO-PCIs is of higher concern given the excessive rate of coronary dissection, perforations, and distal micro-embolizations reported[62, 63].

Another argument used is that successful CTO-PCIs improve prognosis compared to failed CTO-PCIs. This claim is surprising, given that CTO-PCI is the direct determinant of serious complications in the failed cohorts. One could simply argue the other way around that CTO-PCIs in fact worsen the prognosis of patients undergoing failed procedure. The argument used by CTO-PCI promoters is based on pooled observations[64] and is questionable as often retrospective pooled comparisons cannot take into account key differences in baseline characteristics between pooled groups due to lack or non-homogeneous data available. This is supported by the analysis of patients from the CREDO-Kyoto Registry (1192 successful CTO-PCIs vs. 332 failed CTO-PCIs), which in presence of homogenous baseline data available for the entire cohort suggests that at 3-year there is no difference in all-cause mortality between groups[2].

Invasiveness of CTO-PCI

CTO-PCIs are very invasive procedures impacting both at systemic and at coronary/cardiac specific levels. They are associated with very long procedural and fluoroscopic times as well as increased use of contrast volumes and related incidence of renal failure[52-54]. Poor tolerance by sedated patients, complex risk profile, and prolonged procedural time are regarded as factors triggering the adoption of general anaesthesia instead of sedation[65]. The need for significant and prolonged platelet inhibition after CTO-PCI is not a trivial factor. Evidence suggests that patients with extensive coronary stents undergoing non-cardiac surgery early after stenting are at increased risk of MACE, with perioperative mortality rates as high as 85% being reported due to different reasons including stent thrombosis as a result of stopping or changing antiplatelet regime[66, 67].

One of the most concerning aspect of CTO-PCI is its excessive coronary invasiveness, which is unprecedented. This causes serious complications including coronary perforation, dissections, tamponade, acute thrombotic events, LV impairments, and peripheral vascular injuries. The occurrence of these complications is not surprising and probably should be expected when considering the level of coronary invasiveness applied during CTO-PCI, the off-label use of stents designed for non CTO lesions, the CTO-PCI related activation of patho-physiological mechanisms triggering acute thrombosis, chronic inflammation as well as repeated intra-coronary micro-embolization in the relevant viable myocardial territory which may impair LV function in line with the principles of established models of chronic heart failure[68]. Patel *et al.* [55] in a meta-analysis of 18,061 pooled CTO patients with 18,941 target CTOs reported a rate of coronary perforation of 3.65% vs. 10.70%, in successful vs failed CTO-PCIs (P<.001), with a related incidence of tamponade of 0% vs. 1.65% (P <.001). These numbers equal to hundreds of patients suffering poor health outcome caused by CTO-PCI procedures. This is not an isolated observation. Mehran *et al.* [62] reported an analysis from the Multi-national CTO Registry in 1791 CTO patients. The rates of coronary dissection and perforation were of 4.3% and 1.7% and of 9.4% and 7.4% in successful vs. failed CTO-PCI, respectively. Of note, the mortality rate of the failed CTO-PCI cohort was not reported. High rates of MI and need for emergency CABG were reported, but deaths after emergency CABG were omitted (to be ascribed by intention to treat to the failed CTO-PCI cohort). Excessive rates of serious complications have been reported by Japanese centres. Kimura *et al.* [69] in a series of 1014 CTOs in 943 patients compared the antegrade (n=733) vs retrograde (n=277) approaches. They reported extremely high rates of coronary dissection (14.7% vs. 10.1%), perforation (8.2% vs. 13%), and distal myocardial embolization (3.7% vs. 1.4%) in the antegrade vs retrograde cohorts respectively.

The goal of CABG surgery is to position the anastomosis in a health coronary segment distal to the blockage (Figure 4A). Conversely, the goal of CTO-PCI stenting is to perform a variety of "in blockage procedures" including complex antegrade/retrograde wiring, high pressure ballooning, and multiple stenting (i.e. leaving behind foreign bodies triggering continuously in-plaque chronic thrombosis and inflammation) to achieve recanalization (Figure 4B). These technical differences between CABG and CTO-PCI are not trivial and might explain the rates of serious complications reported during CTO-PCI stenting as well as the higher rates of early recurrence, cardiac specific complications, and worse late health outcome. Of note, when referred for emergency CABG failed CTO-PCIs present with rather dramatic findings (Figure 4C) often associated with deaths and/or major complications that are unlikely to be retained in the CTO-PCI cohorts of the observational studies available in the literature[62, 63, 69].

5. Conclusions

Available evidence-based medicine derived from the COURAGE and OAT trials suggest that in patients with stable CAD or in those with occluded coronary arteries < 3 months the use of PCI-stenting is not superior to medical therapy alone. The ongoing DECISION-CTO and the EuroCTO trials once completed will help clarifying the impact of CTO-PCI versus medical therapy alone in these patients.

The use of CTO-PCI is spreading quickly worldwide across CABG anatomical categories such as LMS, LAD, and MVD disease despite the establishment of the Heart Teams and despite strong evidence from large sub-analyses of CABG vs. PCI-stent trials and from large database registries supporting the superiority of CABG. The recent evidence-based medicine SYNTAX trial confirms the superiority of CABG at 1 and 5 years in MACCE events across all the patient categories including large subsets of CTO patients.

The global promotion of CTO-PCI as an effective procedure across all CAD anatomical categories is of concern as it is based on questionable evidence derived only from "comfortable" comparisons between successful vs. failed CTO-PCI procedures with no controls. In fact, these "comfortable" comparisons suggest that CTO-PCI might be causing significant injury to patients suffering procedural failures. This key safety concern seems to be grossly misrepresented in the available CTO-PCI literature while a disproportionate emphasis of efficacy seems to be based on soft findings such as on table successful recanalization, which is neither synonymous of improved myocardial perfusion/function nor evidence of late patency. In this context, the undertaking of randomised trials comparing CABG vs. CTO-PCI in patients with LMS, LAD, and MVD does not seem to be justified on pure clinical grounds at this stage.

On the ground of the available evidence we strongly suggests that all CTO patients should be carefully discussed at multidisciplinary Heart Team meetings including a balanced professional representation of surgeons and interventional cardiologists, bearing in mind that at this stage for CTO patients with LMS, LAD, and MVD disease CTO-PCI may have a role only for a certain type of sick population deemed to be not suitable for CABG.

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None

Figure legends:

Figure 1

Schematic shows possible anatomical locations of CTO lesions. **A**: PCI coronary territory with lumen size 2.0-3.00mm; **B**: CABG coronary territory with lumen size 1.0-2.0mm.

Figure 2

Figure shows a case of multiple CTOs treated with CABG surgery in 2002 at our Institution; pictures are from a coronary angiogram taken in 2015. **A**: native left coronary system showing long CTOs involving the LAD and a Diagonal/Intermediate branches; **B**: patent SVG-Diagonal/Intermediate graft; **C**: patent LIMA-LAD graft. Unpublished data.

Figure 3

Figure shows a case of long CTO of Right Coronary Artery (RCA) treated with CTO-PCI at our Institution. **A-D:** Coronary angiogram taken in late 2013; **A**: long CTO is seen at the mid RCA segment (black arrows); **B-C**: wiring and ballooning of CTO; **D**: on table final result. **E**: Coronary angiogram taken early in 2015. Picture shows recurrence of CTO lesion at mid RCA segment (white arrows). Unpublished data.

Figure 4

Figure shows technical principles of coronary revascularisation and a CTO-PCI complication. **A**: CABG positions coronary anastomoses in a health coronary segments distal to the blockage; **B**: CTO-PCI involves invasive in-plaque procedures; **C**: Epicardial view of a coronary dissection in the proximal LAD (black arrows) requiring emergency CABG following failed CTO-PCI.

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